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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte EDUARDO MARBAN

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Appeal 2019-005766
Application 13/412,051
Technology Center 1600

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Before ERIC B. GRIMES, FRANCISCO C. PRATS, and TAWEN CHANG, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 39 and 58–74. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant states that "[t]he real patties in interest are The Johns Hopkins University, a Maryland corporation, the assignee of this application; and Capricor Therapeutics, Inc., a Delaware corporation, an exclusive licensee of this application from The Johns Hopkins University." Appeal Br. 4.

STATEMENT OF THE CASE

The following rejections are before us for review:

(1) Claims 73 and 74, under pre-AIA 35 U.S.C. § 102(a) as being anticipated by Messina[2] (Final Act. 4–5 (entered January 25, 2018))

(2) Claims 39, 58–63, and 70–74, under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Messina,[3] Heng,[4] and Harvey[5] (Final Act. 5–10);

(3) Claims 64–66, under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Messina, Heng, Harvey, Beltrami,[6] and Piper[7] (Final Act. 11–12); and

(4) Claims 64–69, under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Messina, Heng, Harvey, Piper, and Beltrami (Final Act. 13–14).

Claims 39, 73, and 74, the independent claims on appeal, read as follows:

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[2] Elisa Messina et al., *Isolation and Expansion of Adult Cardiac Stem Cells From Human and Murine Heart*, 95 CIRCULATION RESEARCH 911–921 (2004).
[3] WO 2009/087087 A1 (published July 16, 2009).
[4] Boon Chin Heng et al., *Strategies for directing the differentiation of stem cells into the cardiomyogenic lineage in vitro*, 62 CARDIOVASCULAR RESEARCH 34–42 (2004).
[5] Richard P. Harvey, *Molecular Determinants of Cardiac Development and Congenital Disease* (Chapter 16), MOUSE DEVELOPMENT 331–370 (2002).
[6] Antonio P. Beltrami et al., *Adult Cardiac Stem Cells Are Multipotent and Support Myocardial Regeneration*, 114 CELL 763–776 (2003).
[7] H. Michael Piper et al., *Determinants of Cardiomyocyte Development in Long-term Primary Culture*, 20 J. MOL. CELL. CARDIOL. 825–835 (1988).

39. A method of treating a subject having diseased or damaged cardiac tissue, the method comprising administering to the subject a therapeutically effective amount of cardiosphere-derived cells (CDCs),

wherein said CDCs are a population of cells obtained by plating and expanding cardiospheres (CSps) as an adherent monolayer culture on a solid surface of a culture vessel; and

wherein said CDCs are not further manipulated to form secondary cardiospheres (IICSps).

73. A method of treating a subject having diseased or damaged cardiac tissue, the method comprising administering to the subject a therapeutically effective amount of cardiosphere-derived cells (CDCs), wherein said CDCs are a population of cells obtained by:

collecting cardiospheres (CSps);

plating said CSps onto a culture vessel; and

expanding said CSps as an adherent monolayer culture on a solid surface of said culture vessel to form said therapeutically effective amount of said CDCs.

74. A method of treating a subject having diseased or damaged cardiac tissue, the method comprising administering to the subject a therapeutically effective amount of cardiosphere-derived cells (CDCs), wherein said CDCs are a population of cells obtained by plating and expanding cardiospheres (CSps) as an adherent monolayer culture on a solid surface of a culture vessel.

Appeal Br. 27–29.

ANTICIPATION

It is well settled that a reference can only anticipate a claim if it discloses all the claimed limitations "arranged or combined in the same way as in the claim." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,* 683 F.3d 1356, 1361 (Fed. Cir. 2012) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.,* 545 F.3d 1359, 1370 (Fed. Cir. 2008)).

In the present case, we agree with Appellant that Messina does not anticipate claims 73 and 74. In particular, we agree with Appellant that Messina does not disclose administering the same product as recited in Appellant's claims 73 and 74.

Claim 73 recites administering, to a subject with diseased or damaged cardiac tissue, "cardiosphere-derived cells (CDCs)." Appeal Br. 28. Claim 73 requires the CDCs to be "a population of cells obtained by: collecting cardiospheres (CSps); plating said CSps onto a culture vessel; and expanding said CSps as an adherent monolayer culture on a solid surface of said culture vessel." *Id.*

Similarly, claim 74 recites administering CDCs, "wherein said CDCs are a population of cells obtained by plating and expanding cardiospheres (CSps) as an adherent monolayer culture on a solid surface of a culture vessel." Appeal Br. 29.

Appellant's Specification explains that cardiospheres, from which the CDCs of claims 73 and 74 are derived, are clusters of cells that spontaneously generate when processed cardiac tissue is cultured in a specific fashion. *See* Spec. ¶¶ 145, 222. Once removed from the initial culture, the cardiospheres may be maintained in poly-D-lysine-coated dishes. *See id.* ¶ 222.

To obtain the CDCs recited in claims 73 and 74, the cardiosphere clusters are disaggregated and then cultured in fibronectin-coated vessels, which results in formation of an adherent monolayer of cells on the vessels' fibronectin-coated surface. *See* Spec. ¶ 145 ("In several embodiments, growth on the surface is monolayer growth. ***These cells are cardiosphere-derived cells (CDCs)***.") (emphasis added).

Appellant's Specification, thus, distinguishes between cardiospheres, which are populations of cells that have a clustered structure, and cardiosphere-derived cells (i.e. CDCs as recited in claims 73 and 74), which are populations of cells that have been induced to form an adherent monolayer, a structure distinct from a clustered structure.

Rather than administering CDCs as recited in claims 73 and 74, Messina discloses administering *cardiospheres* to mice having experimentally induced myocardial infarctions. *See* Messina 916–917 ("[T]hawed (cryopreserved) adult human CSs [cardiospheres] from three atrial (one male and two female) and one ventricular (one female) biopsy specimens were injected into the viable myocardium bordering a freshly produced infarct.").

As Appellant contends, and the Examiner does not dispute, Messina's cardiospheres are made by substantially the same process as the process described in Appellant's Specification, and have the same clustered structure as the cardiospheres described in Appellant's Specification. *See* Appeal Br. 13–14; *see also* Messina 192 (describing Messina's cardiospheres as "clusters of small, round, phase-bright cells").

Thus, when Messina describes administering cardiospheres to infarcted mice, Messina describes administering a population of cells that

has a clustered structure. As discussed above, however, and explained in Appellant's Specification, the CDCs of claims 73 and 74 do not have cardiospheres' clustered structure. We are not persuaded, therefore, that in administering cardiospheres to infarcted mice, Messina describes administering same product (CDCs) as recited in claims 73 and 74.

As Appellant contends, moreover, CDCs have a distinct expression profile of growth factors as compared to cardiospheres. *See* Appellant's Fig. 18A–C; *see also* Spec. 283 ("FIG. 18 shows two representative blots (18A) from cardiospheres and CDCs derived from the same patient sample, together with the corresponding densitogram (l8B and 18C), showing the cardiosphere/CDC optical density ratios for each [growth] factor."). And, as Appellant also contends, the level of β-catenin expression in CDCs is significantly different than in cardiospheres. *See* Ibrahim Decl. ¶ 4.[8]

Thus, to summarize, Appellant's Specification distinguishes between cardiospheres, which are populations of cells that have a clustered structure, and cardiosphere-derived cells (i.e. CDCs as recited in claims 73 and 74), which are populations of cells that have been induced to form an adherent monolayer, a structure distinct from a clustered structure. And, evidence of record shows that cardiospheres and CDCs have different protein expression profiles. We therefore agree with Appellant that the cardiospheres administered by Messina to mice are not the same product as the CDCs administered to subjects in Appellant's claims 73 and 74. We also agree with Appellant, therefore, that Messina does not anticipate claims 73 and 74.

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[8] Declaration of Ahmed Ibrahim, Ph.D., under 37 C.F.R. § 1.132 (signed October 28, 2016).

We recognize, as the Examiner contends, that the CDCs recited in claims 73 and 74 are recited using product-by-process language, which encompasses any identical prior art product, regardless of whether the prior art product is made by the process recited in the claims. *See In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). The Examiner, however, points to no persuasive evidence suggesting that the cardiospheres administered by Messina are identical to the population of cells, CDCs, administered in the processes of claims 73 and 74. Indeed, as discussed above, the evidence of record supports Appellant's contention that cardiospheres and CDCs are distinct populations of cells with distinct properties.

In sum, for the reasons discussed, we agree with Appellant that Messina does not disclose administering the same populations of cells as recited in Appellant's claims 73 and 74. We therefore reverse the Examiner's rejection of claims 73 and 74 as anticipated by Messina.

OBVIOUSNESS

In rejecting claims 39, 58–63, and 70–74 over Messina, Heng, and Harvey, the Examiner again cited Messina as describing a process of administering CDCs to treat damaged cardiac tissue. Final Act. 7.

The Examiner conceded that Messina differs from the rejected claims in two respects: (1) "Messina et al do not expressly teach wherein the administered CDCs had not been further manipulated to form secondary cardiospheres" and (2) "Messina et al do not expressly teach wherein the cardiospheres were disaggregated before plating and expanding as an adherent monolayer culture on a solid surface." Final Act. 8.

The Examiner cited Heng and Harvey as evidence that it would have been desirable to culture Messina's cardiospheres in the presence of

fibronectin, which the Examiner asserts, based on Appellant's Specification, would inherently yield the adherent monolayer of cells recited in the rejected claims. Final Act. 8–10.

We reverse this rejection as well. Consistent with the Examiner's contention, and as noted above, Appellant's Specification discloses that an adherent monolayer of CDCs results when cardiospheres are cultured in a vessel in which the surface is coated with fibronectin. *See* Spec. ¶ 145.

As the Examiner also found, Heng discloses that, when using stem cells to treat infarcted animals, it is advantageous for the cells to have at least some limited degree of differentiation:

> There is a strong possibility that some degree of cardiomyogenic differentiation of stem cells in vitro prior to transplantation would result in higher engraftment efficiency, as well as enhanced myocardial regeneration and recovery of heart function. Additionally, this may also alleviate the probability of spontaneous differentiation of stem cells into undesired lineages and reduces the risk of teratoma formation, in the case of embryonic stem cells.

Heng 34 (abstract).

As the Examiner found, Heng discloses that fibronectin is among a number of extracellular matrix (ECM) proteins that may induce differentiation of cardiac stem cells:

> [T]he introduction of appropriate extracellular matrix molecules within in vitro culture would certainly enhance the directed differentiation of stem cells into the cardiomyogenic lineage. With commonly used ECM supplements in cell culture, such as collagen, laminin and fibronectin, there was reported to be enhanced myofibrillogenesis, spontaneous contractile activity and differentiated morphology of neonatal cardiomyocytes cultured in vitro. It is likely that such supplemented ECM molecules would also be beneficial for the cardiomyogenic differentiation of stem cells, although there are as yet no

> reported studies. Other ECM molecules that were shown to play an important role in cardiomyogenic differentiation in histological studies include Syndecan-4[,] Tenascin C [,] and hyaluronic acid. However, the effects of these molecules on the in vitro culture of primary cardiomyocytes, as well as the cardiomyogenic differentiation of stem cells remain to be investigated.

Heng 37 (citations omitted).

As noted above, however, to induce formation of an adherent monolayer of CDCs, Appellant's Specification discloses that the fibronectin must be coated onto the surface of the culture vessel. *See* Spec. ¶ 145.

Thus, although we acknowledge Heng's disclosure that including fibronectin in stem cell culture medium can aid in differentiation, the Examiner does not identify any teaching in Heng specifically suggesting that the fibronectin should be coated onto the surface of the culture vessel. Absent impermissible hindsight, therefore, we are not persuaded that Heng would have suggested culturing Messina's cardiospheres in a fibronectin-coated vessel, so as to produce an adherent monolayer of CDCs, as recited in the rejected claims.

We acknowledge Harvey's disclosure, identified by the Examiner, that during embryonic cardiac development "[t]he timing and direction of movement of cardiac progenitors toward the midline depends on the graded distribution of fibronectin in extracellular matrix, deposited at the mesodermal/endodermal interface." Harvey 340 (citation omitted). We are not persuaded, however, that Harvey's disclosure regarding cell movement in a developing embryo would have suggested culturing Messina's cardiospheres in a fibronectin-coated vessel, even when viewed in combination with Heng.

In sum, for the reasons discussed, the Examiner does not persuade us that the combined teachings of Messina, Heng, and Harvey, would have suggested culturing Messina's cardiospheres in a fibronectin-coated vessel, so as to produce an adherent monolayer of CDCs, as recited in claims 39, 58–63, and 70–74. We therefore reverse the Examiner's rejection of claims 39, 58–63, and 70–74 over Messina, Heng, and Harvey.

In rejecting claims 64–69 over Messina, Heng, Harvey, Piper, and Beltrami, the Examiner cited Piper and Beltrami as evidence that additional features recited in claims 64–69 would have been obvious variations of the process suggested by the combination of Messina, Heng, and Harvey. *See* Final Act. 11–14. Because Piper and Beltrami do not remedy the deficiencies discussed above in the combination of Messina, Heng, and Harvey, we also reverse the Examiner's rejections of claims 64–69.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed
73, 74	102(a)	Messina		73, 74
39, 58–63, 70–74	103(a)	Messina, Heng, Harvey		39, 58–63, 70–74
64–66	103(a)	Messina, Heng, Harvey, Beltrami, Piper		64–66
64–69	103(a)	Messina, Heng, Harvey, Piper, Beltrami		64–69
Overall Outcome				39, 58–74

REVERSED